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ORIGINAL ARTICLE

The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: A validation study on a Turkish patient population in different age categories

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Abstract We investigated an optimal cutoff level of free/total PSA ratios (f/t PSA) in predicting prostate cancer in different age groups, focusing on the avoidance of unnecessary prostate biopsies. A total of 4955 men were enrolled into the study. Serum tPSA, fPSA, and f/t PSA ratios were determined for the study population. All males who had suspicious digital rectal examination and tPSA > 4 ng/mL underwent transrectal ultrasonography-guided prostate biopsy. Receiver operating characteristic (ROC) curves for each group were generated by plotting the sensitivity versus 1-specificity for the f/t PSA ratio. The sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were obtained using various f/t PSA ratio cutoffs for different age groups. There were 657 patients with a PSA level of 4–10 ng/mL. According to sensitivity and specificity f/t% PSA cutoff points were determined to be 10%, 15%, 15%, and 10% in 50–59 years, 60–69 years, >70 years, and all ages categories, respectively, in patients with initial PSA level of 4–10 ng/mL. f/t PSA ratio had an area under the curve (AUC) value of 0.81 (95% confidence level: 0.80–0.82) for all age groups in detecting prostate cancer.

Conflicts of interest: All authors declare no conflicts of interest.

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f/t PSA ratio has an AUC value of 0.669 (0.632—0.705) in detecting prostate cancer among patients with a PSA level of 4—10 ng/mL. Ten percent of f/t PSA ratio had the highest specificity with PLR and 30% f/t PSA ratio had the highest sensitivity with lower NLR in the all-age categories. The current study shows that the use of f/t PSA ratio in patients with PSA levels of 4—10 ng/mL should enhance the specificity of PSA screening and decrease the number of unnecessary biopsies. The age-related changes warrant further investigation in a large, multicentric, and multinational population to improve the clinical use of f/t PSA cutoffs.

Introduction

Serum prostate-specific antigen (PSA) is a useful biomarker for screening of prostate cancer and monitoring patients for disease progression [1,2]. Oesterling et al. [3] established age-specific reference ranges for serum PSA levels to improve its sensitivity in younger men and to increase its specificity in older men [3]. However, recent findings emphasize the limitation of these PSA threshold values to discriminate between prostate cancer and benign disease in asymptomatic men [4—6]. Since the identification of free PSA (fPSA) by Stenman et al. [7], Lilja et al. [8], many retrospective and prospective studies have shown the usefulness of the free/total (f/t) PSA ratio for differentiating benign disease (BD) and prostate cancer in gray-zone patients who have PSA levels of 4—10 ng/mL in which BD and cancers overlap. Despite the various cutoff levels defined in different studies and our previous article for f/t PSA, the cutoff levels for f/t PSA ratios specified for different age groups have not yet been determined as tPSA [9—15].

The aim of this study was to evaluate the efficacy and limitation of f/t PSA ratios in different age groups and to determine cutoff levels for any age in a large scale. Some controversy exists regarding the clinical benefits of f/t PSA because the large overlap between prostate cancer and BD for various f/t PSA cutoff levels provides conflicting data for the correlation between f/t PSA and a pathologic outcome.

Methods

The study population comprised 4955 subjects who underwent PSA-based prostate cancer screening in our institution. Blood samples were drawn before any prostatic manipulation after each patient provided informed consent. tPSA and fPSA levels were measured in fasting peripheral blood samples. Serum PSA levels were analyzed by immunometric assay (Immulite 2000, DPC, Los Angeles, CA, USA) with analytical sensitivity of 0.04 ng/mL. Serum fPSA levels were analyzed using a solid phase, two-site sequential chemiluminescent immunometric assay (Immulite 2000, DPC) with analytical sensitivity of 0.02 ng/mL. The intra- and interassay coefficients of variations (CVs) were below 5.0 % for total and free PSA.

Men age 40—80 years were included of the study. Exclusion criteria were as follows: $<$40 years and $>$80 years, diagnosis of active urinary tract infection or other systemic infection, acute and urinary retention. Also excluded were patients who had underwent newly urethral catheterization or cystoscopy.

All patients who had a suspicious digital rectal examination (DRE) and/or total PSA levels $>$ 4 ng/mL underwent transrectal ultrasonography (TRUS) and 12 core peripheral zone biopsies were taken [16]. The samples were evaluated by two pathologists to maintain consistency in the diagnosis of prostate cancer. fPSA and tPSA levels were analyzed for each sample. Serum tPSA, fPSA, and f/t PSA ratios were determined for the study population.

Statistical analysis

Study data was analyzed in Medcalc 10.0 software (Chicago, IL, USA). Continuous data were expressed as mean $\pm$ standard deviation or median, 95% confidence interval (95% CI) was used if distribution was not normal, and categorical data were presented as rates. Comparison of two groups was performed by Mann-Whitney *U* test because of abnormal distribution of fPSA and tPSA levels. The Kolmogorov-Smirnov test was used to check the normal distribution. Sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio was calculated by receiving operating characteristic (ROC) curve analysis to determine the diagnostic performance of f/t PSA ratios in detecting prostate cancer. Values of area under the curve (AUC) were also calculated by ROC analysis. All the hypotheses were constructed as two tailed and an α value of 0.05 was accepted as significant.

Results

A total of 4955 patients were enrolled into the study with a mean age of 63.3 $\pm$ 11.3 years. Prostate cancer was detected in 109 patients (2.2%). There were no patients $<$50 years of age in whom prostate cancer was diagnosed, 15 patients (13.7%) were aged between 50 years and 59 years, 38 patients (34.9%) were aged between 60 years and 69 years, and 56 patients (51.4%) were $>$70 years of age ($p < 0.001$). Of 109 cancers, 7%, 53%, 36%, 2%, and 2% had a Gleason score of 5, 6, 7, 8, and 9, respectively. In patients with prostate cancer, 43%, 30%, 26%, and 1% had a clinical stage T1c, T2a, T2b, and T3, respectively. Forty-four men (40%) had undergone radical retropubic prostatectomy, 59 (54%) had received radiation therapy, and 6 (6%) had received hormonal therapy.

The median fPSA levels for patients with prostate cancer and benign histological findings were 1.36 ng/mL (95% CI:

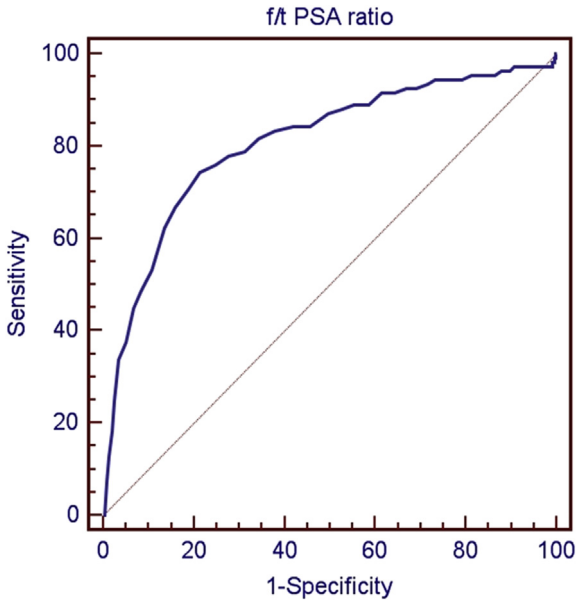

Figure 1. Receiver operating characteristic curve of f/t prostate-specific antigen (PSA) ratio for all age groups in 4955 patients.

1.1—1.6) and 0.34 ng/mL (95% CI: 0.33—0.35), respectively ($p < 0.0001$). The median tPSA levels for patients with prostate cancer and benign histological findings were 10.1 ng/mL (95% CI: 7.3—13.9) and 1.3 ng/mL (95% CI: 1.2—1.3), respectively ($p < 0.0001$). f/t PSA ratio had an AUC value of 0.81 (95% CI: 0.80—0.82) for all age groups in detecting prostate cancer. f/t PSA ratio of 10% had a specificity of 95% (95% CI: 94—95) with a PLR of 7.6, and f/t PSA ratio of 30% had a sensitivity of 91.7% (95% CI: 85—96) with a NLR of 0.23 in all age groups. Fig. 1 displays the ROC curve of f/t PSA ratio for all age groups in 4955 patients for detecting prostate cancer.

Ten percent of f/t PSA ratio had the highest specificity and PLR in the age categories; 50—59 years, 60—69 years, and ≥70 years. Ten percent f/t PSA ratio had a specificity of 95.5% (95% CI: 94—97), 95.7% (95% CI: 94—97), 93.1% (95% CI: 92—94), and PLR of 7.3 (3.6—15), 7.9 (5.1—12.2), and 6 (4.4—8.2) in age categories 50—59 years, 60—69 years, and ≥70 years, respectively (Table1). Thirty percent f/t PSA ratio had the highest sensitivity with lower NLR in the all age categories. Thirty percent f/t PSA ratio had a sensitivity of 93.3% (95% CI: 68—99), 94.7% (95% CI: 82—99), 89.3% (95% CI: 78—96), and a NLR of 0.18 (95% CI: 0.03—1.2), 0.16 (95% CI: 0.04—0.6), and 0.31 (0.1—0.7) in age categories 50—59 years, 60—69 years, and ≥70 years, respectively. Table 1 displays the diagnostic performance of f/t PSA ratios according to the age categories.

Table 1 Sensitivity, specificity, and likelihood ratios of f/t prostate-specific antigen ratios in all patients according to the age categories.

f/t PSA ratio	50—59 y	60—69 y	≥70 y
95% CI			
f/t PSA 10%			
Sensitivity	33.3 (12—62)	34.2 (20—51)	41 (28—55)
Specificity	95.5 (94—97)	95.7 (94—97)	93.1 (92—94)
PLR	7.3 (3.6—15)	7.9 (5.1—12.2)	6 (4.4—8.2)
NLR	0.7 (0.5—1.1)	0.69 (0.5—1)	0.63 (0.5—0.8)
f/t PSA 15%			
Sensitivity	66.7 (38—88)	63.2 (46—78)	69.6 (56—81)
Specificity	85.4 (84—87)	83.1 (81—85)	81.7 (80—84)
PLR	4.6 (3.2—6.6)	3.8 (2.9—4.8)	3.8 (3.2—4.5)
NLR	0.39 (0.2—0.8)	0.44 (0.3—0.7)	0.37 (0.2—0.6)
f/t PSA 20%			
Sensitivity	80 (52—95)	79 (63—90)	78.6 (66—88)
Specificity	71.2 (69—74)	66 (63—69)	66.5 (64—69)
PLR	2.8 (2.2—3.6)	2.3 (2—2.7)	2.4 (2—2.7)
NLR	0.28 (0.1—0.8)	0.32 (0.2—0.6)	0.32 (0.2—0.5)
f/t PSA 25%			
Sensitivity	86.7 (60—98)	89.5 (75—97)	85.7 (74—94)
Specificity	52.4 (50—55)	46.8 (44—50)	48.9 (46—52)
PLR	1.8 (1.5—2.2)	1.7 (1.5—1.9)	1.7 (1.5—1.9)
NLR	0.25 (0.07—0.9)	0.23 (0.09—0.6)	0.29 (0.2—0.6)
f/t PSA 30%			
Sensitivity	93.3 (68—99)	94.7 (82—99)	89.3 (78—96)
Specificity	36.9 (34—-39)	32.7 (30—35)	34.2 (31.8—37)
PLR	1.5 (1.3—1.7)	1.4 (1.3—1.6)	1.4 (1.2—1.5)
NLR	0.18 (0.03—1.2)	0.16 (0.04—0.6)	0.31 (0.1—0.7)

CI = confidence interval; f/t = free/total; NLR = negative likelihood ratio; PLR = positive likelihood ratio; PSA = prostate-specific antigen.

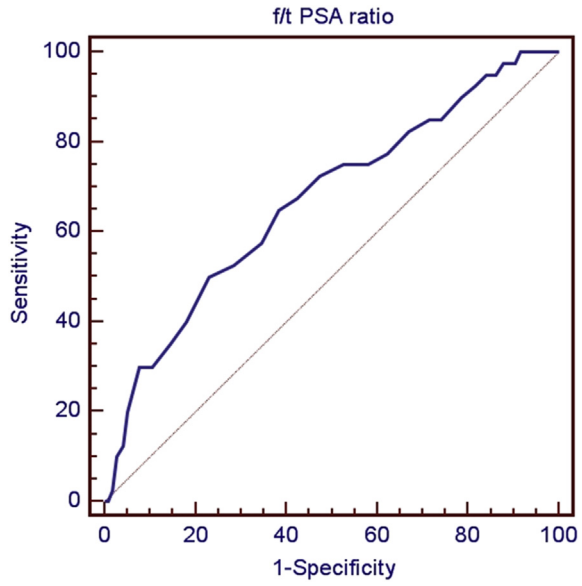

Figure 2. Performance of f/t prostate-specific antigen (PSA) ratio in 657 patients with a PSA level of 4—10 ng/mL.

There were 657 patients with a PSA level of 4—10 ng/mL. Forty of these patients (6%) had received a diagnosis of prostate cancer. f/t PSA ratio has an AUC value of 0.669 (0.632—0.705) in detecting prostate cancer among patients with a PSA level of 4—10 ng/mL. Fig. 2 displays the ROC curve of f/t PSA ratio in patients with PSA level of 4—10 ng/mL. Lower f/t PSA ratios had higher specificity and PLRs and higher f/t PSA ratios were related to better sensitivity and NLRs. Table 2 displays the performance of f/t PSA ratios in age categories with a PSA level of 4—10 ng/mL.

Discussion

PSA is one of the most important biomarkers for detecting prostate cancer and guiding decisions to biopsies of the prostate. Despite its adequate sensitivity, the use of PSA testing is limited by a significant lack of specificity, which can result in unnecessary biopsies. Use of the f/t PSA ratio has been shown to improve specificity in detection of prostate cancer. No definitive data are available indicating the optimal %f/tPSA that should be applied.

Denham et al. [17] reported that the ratio f/t PSA holds no benefit in discriminating between a patient with prostate cancer and a patient with benign prostatic hiperplasia. In contrast to this report, previous studies and our reports have demonstrated that at the PSA levels of 4.0—10.0 ng/mL, the ratio of f/t PSA significantly improves discrimination between prostate cancer and benign conditions and helps identify the need for prostate biopsy and avoid unnecessary biopsies [15,17—22].

Table 2 Sensitivity, specificity, and likelihood ratios of f/t prostate-specific antigen ratios in patients with a prostate-specific antigen level of 4—10 ng/mL according to the age categories.

f/t PSA ratio	50—59 y	60—69 y	≥70 y
95% CI			
f/t PSA 10%			
Sensitivity	41.6 (15—72)	14.3 (2—43)	35.7 (13—65)
Specificity	84.7 (76—91)	90.4 (85—94)	90.6 (87—93)
PLR	2.7 (1.4—5.3)	1.49 (0.4—5.4)	3.8 (1.9—7.7)
NLR	0.69 (0.4—1.3)	0.95 (0.6—1.5)	0.71 (0.4—1.2)
f/t PSA 15%			
Sensitivity	75 (43—95)	50 (23—77)	50 (23—77)
Specificity	53 (43—63)	58.5 (51—66)	73.8 (69—79)
PLR	1.6 (1.1—2.3)	1.2 (0.7—2.1)	1.9 (1.1—3.2)
NLR	0.47 (0.2—1.3)	0.85 (0.5—1.5)	0.68 (0.4—1.2)
f/t PSA 20%			
Sensitivity	83.3 (52—98)	78.6 (49—95)	64.3 (35—87)
Specificity	25.5 (17—35)	32.5 (26—40)	53.8 (48—60)
PLR	1.1 (0.7—1.7)	1.16 (0.8—1.6)	1.4 (0.9—2.1)
NLR	0.65 (0.2—2.3)	0.66 (0.2—1.8)	0.66 (0.3—1.4)
f/t PSA 25%			
Sensitivity	91.7 (62—100)	92.9 (66—100)	85.7 (57—98)
Specificity	5.1 (1.7—12)	13.8 (9—20)	31.2 (26—37)
PLR	0.97 (0.4—2.3)	1.08 (0.7—1.6)	1.25 (1—1.6)
NLR	1.63 (0.2—10.7)	0.52 (008—3.4)	0.46 (0.1—1.7)
f/t PSA 30%			
Sensitivity	100 (74—100)	100 (77—100)	92.9 (66—100)
Specificity	1 (0.03—5.6)	2.66 (0.9—6.1)	16.6 (13—21)
PLR	1 (0.1—7.1)	1.03 (0.4—2.4)	1.11 (0.8—1.5)
NLR	0	0	0.43 (0.07—2.9)

CI = confidence interval; f/t = free/total; NLR = negative likelihood ratio; PLR = positive likelihood ratio; PSA = prostate-specific antigen.

Partin et al. [23] suggested using f/t PSA ratio $\leq$ 15, which would detect all advanced, nonorgan confined, and large volume tumors, while avoiding 80% of biopsies in men with insignificant disease, particularly in the intermediate range of total PSA (4.1—10 ng/mL).

Catalona et al. [11] suggested a cutoff of $\leq$24% to detect 90% of cancers and to avoid 18% of benign biopsy findings in patients with a PSA value 2.6—4.0 ng/mL. In an update, Catalona et al. [18] examined a variety of cutoffs, some of which were as low as 10%. Other investigators have recommended cutoffs of 18—27%. Chun et al. [24] demonstrated that median f/t PSA ratio as most men had f/tPSA values of >25% in Canadian men. Suzuki et al. [14] reported that using a cancer probability cutoff level of 10% provides a 26% reduction in the number of unnecessary biopsies while maintaining a sensitivity of 90%. Their results are in contrast to our findings and those of other studies [18—27]. In the current study, a 10% cutoff had a sensitivity of 37.6% and specificity of 95% in all age groups. Table 2 shows an increasing trend for specificity with decreasing f/t PSA ratios in age categories of patients with tPSA of 4—10 ng/mL. These results are correlated with those of Catalona et al. [18] and other studies [19—22,25,26].

Age-specific reference rates have been proposed as a means of improving specificity and positive predictive value of the total PSA in screening for prostate cancer. Previous studies demonstrated that the total PSA level is significantly related to age; however, an age-specific f/t PSA ratio has not yet been determinated. Chun et al. [24] hypothesized that a relationship between f/tPSA ratio and age can be established [24].

Age-specific cutoffs were also reported by Catalona et al. [18] as 20%, 26%, and 28% f/t PSA ratios for ages 50—59 years, 60—69 years, and 70—75 years, respectively. In the current study, the f/t% PSA cutoff points were determined to be 10%, 15%, 15% and 10% in 50—59 years, 60—69 years, >70 years, and all ages categories, respectively (Table 2). Ten percent f/t PSA ratio had the highest specificity and PLR in the all age categories. Thirty percent f/t PSA ratio had the highest sensitivity and a lower NLR in the same age categories. These results are correlated with our previous study [15]. However, the cutoff values determined in the current study display inconsistency with the report by Catalona et al. [18]. A possible reason for the different cutoff values could be the use of different assays. In addition, this may be a result of using different statistical approaches. Catalona et al. used high sensitivity as the selection criterion for determining cutoff values. However, sensitivity is a factor used to exclude the disease in the clinical practice. In addition to sensitivity, we also recommended the use of specificity and PLR for determining cutoff values. The PLR predicts the posttest probability. A high PLR avoids unnecessary biopsies and strongly predicts disease in the gray zone.

Contradictory results in the aforementioned studies may also be related to multiple variables, such as significant degradation during frozen storage, study design, sample size, cancer prevalence, assay differences, and many other parameters, in addition to different statistical approaches [27].

Our data are based almost entirely on Turkish men, not accounting for racial variability. The omission of race may limit the applicability of our findings. Our study has other limitations; prostate volumes were not calculated. Several authors have suggested that in patients with large prostates, the determination of f/t PSA ratio lacks specificity in discriminating prostate cancer and benign prostatic hyperplasia [28,29].

In conclusion, the current study shows that the use of f/t PSA ratio in patients with PSA levels of 4—10 ng/mL should enhance the specificity of PSA screening and decrease the number of unnecessary biopsies. Ten percent f/t PSA ratio had the highest specificity with PLR and 30% f/t PSA ratio had the highest sensitivity and a lower NLR in the all age categories. According to sensitivity and specificity, f/t% PSA cutoff points were determined to be 10%, 15%, 15%, 10% in age categories 50—59 years, 60—69 years, >70 years, and all ages categories in patients with initial PSA level of 4—10 ng/mL. The choice of the best cutoff for the f/t PSA ratio depends on a variety of arguments that mainly include the combination of screening modalities used. The age-related changes warrant further investigations in a larger, multicentric and multinational population to improve the clinical use of f/t PSA cutoffs.

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